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## THE INFLUENCE OF THORIUM X ON ANTIBODY-FORMATION

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In 1902 Rutherford and Soddy<sup>1</sup> obtained a highly radioactive filtrate by precipitating thorium from solution with ammonia. Evaporated to dryness, the ammonia being driven off by ignition, this filtrate left a small residue, which weight for weight was several times more active than the original compound. The active constituent secured in this way they called thorium X.

In spite of the great activity of thorium X, its biologic effects were not studied to any extent until about 1912. At the present time we are interested especially in its action on the blood and its organs. Indeed, the most striking effect of thorium X when introduced into the body is leukopenia and disappearance of cells from the marrow. The changes have been studied mostly in the rabbit. Pappenheim and Plesch<sup>2</sup> concluded that it has a toxic effect on the leukocytes in the blood, the marrow cells, for both of which it seemed to have a direct selective affinity, the cells of the spleen, the lymph nodes, the liver and the kidney. Hirschfeld and Meidner<sup>3</sup> found that in large doses it affected all leukocytes practically alike and caused also a slight decrease in the red corpuscles and the hemoglobin. Arneth<sup>4</sup> and Rosenow<sup>5</sup> studied the changes in the leukocytes by thorium X, and Rosenow likened the effect to that of the roentgen ray, but Mello<sup>6</sup> maintains that thorium X has less effect on the lymphoid cells and more on the myelogenous than the roentgen ray. Pappenheim<sup>7</sup> has likened the action of thorium X on the blood to that of benzene. It is noteworthy that thorium X may cause an extreme leukopenia while the red corpuscles and hemoglobin appear to suffer but little, although it is possible that there may be

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<sup>1</sup> Rutherford: *Radioactive Substances and Their Radiations*, 1913.

<sup>2</sup> *Folia Haematologica*, 1912, 14, p. 172; *Ztschr. f. exper. Path. u. Therap.*, 1912, 12, p. 185.

<sup>3</sup> *Berl. klin. Wehnschr.*, 1912, 69, p. 1343.

<sup>4</sup> *Deutsch. med. Wehnschr.*, 1913, 39, p. 733.

<sup>5</sup> *Ztschr. f. ges. exp. Med.*, 1913, 3, p. 385.

<sup>6</sup> *Ztschr. f. klin. Med.*, 1914, 81, p. 285; *Arch. Brasil. de Med.*, 1919, 9, p. 123.

<sup>7</sup> *Ztschr. f. exper. Path. u. Therap.*, 1914, 15, p. 39.

such effective stimulus of production as to conceal the destruction of red corpuscles going on at the same time (Mello<sup>6</sup>). With respect to the substances concerned in immunity reactions, Lippmann and Plesch<sup>8</sup> report that the complement remains apparently unchanged even when practically all the circulating leukocytes have been destroyed by thorium X. Fränkel and Gumpertz<sup>9</sup> observations on the effect of thorium X on the production of typhoid agglutinin did not yield any striking results except that in animals receiving large doses the production seemed to be reduced. Corper<sup>10</sup> found that one-half the lethal amount of thorium X given seven days before or coincident with either the primary or secondary injection, had no effect on the anaphylactic reaction in guinea-pigs. Further, that repeated smaller doses, sufficient in many cases to maintain a leukopenia at about 2,000 during the incubation period, had no recognizable effect on anaphylaxis. Here may be mentioned too that Corper<sup>11</sup> could not influence the course of experimental tuberculosis in guinea-pigs by means of thorium X, and Hirschfeld and Meidner<sup>12</sup> did not succeed in modifying the growth of tumors with it. Corper, however, finds that thorium X in mice greatly increases the virulence of pneumococci and hemolytic streptococci (unpublished).

In connection with certain other experiments, we have made observations on the liberation of antibodies in rabbits under the influence, in varying degrees, of thorium X which is given easily in salt solution. The radiothorium from which the thorium X we have used was prepared was donated by Dr. H. W. McCoy, of the Carnotite Reduction Company, Chicago. The method of determination of dosage is described by Corper.<sup>11</sup> The antigen used was sheep blood, injected intraperitoneally in one dose of 25 c c, as we were familiar with its antigenic effects when so injected.

First, large doses of thorium X were given so that a marked reduction of leukocytes in the peripheral blood was maintained for a few days before the injection of the antigen as well as throughout the period ordinarily required by the antigen to produce its maximum effect as measured by newly formed lysin and precipitin in the blood. For this purpose one-fifth the lethal doses of thorium X was injected intravenously followed by further injections every two or three days

<sup>6</sup> Ztschr. f. Immunitätsforsch. u. exper. Therap., 1913, 17, p. 548.

<sup>8</sup> Berl. klin. Wchnschr., 1914, 51, p. 209.

<sup>10</sup> Jour. Infect. Dis., 1919, 25, p. 248.

<sup>11</sup> Am. Rev. Tuberc., 1918, 2, p. 587.

<sup>12</sup> Ztschr. f. klin. Med., 1913, 78, p. 407.

of from one-fifth to one-twentieth the lethal dose as required. The results, which were practically the same in the five rabbits studied, are illustrated in table 1, and they indicate that while lysin for sheep corpuscles was set free in large amounts, the production of precipitin for sheep protein was reduced very much.

TABLE 1

REPEATED LARGE DOSES OF THORIUM X BEGUN 8 DAYS BEFORE INJECTION OF SHEEP BLOOD

Days After First Injection of Thorium X	Days After Injection of Sheep Blood	Rabbit 2			Control	
		Precipitin	Lysin	Leukocytes	Precipitin	Lysin
0	..	...	.....	15,000		
3	..	...	.....	7,250		
5	..	...	.....	3,500		
7	..	...	.....	1,875		
8	0	0	192			
10	4	0	768	3,250	0	768
12	6	0	6,144	1,750	50	6,144
14	8	800	25,000	1,650	800	6,144
16	10	800	25,000	2,500	1,600	6,144
18	12	400	25,000	1,125	6,400	12,288
20	14	0	25,000	1,425	12,800	6,144
22	16	800	25,000	1,750	12,800	6,144
24	..	...	.....	1,500		

TABLE 2

REPEATED SMALL DOSES OF THORIUM X BEGUN 3 DAYS BEFORE INJECTION OF SHEEP BLOOD

Days After First Dose of Thorium X	Days After Injection of Sheep Blood	Rabbit 1			Rabbit 5			Rabbit 6			Control	
		Precipitin	Lysin	Leukocytes	Precipitin	Lysin	Leukocytes	Precipitin	Lysin	Leukocytes	Precipitin	Lysin
1	..	.....	.....	7,750	.....	.....	13,250	.....	.....	9,750		
4	1	.....	.....	8,250	.....	.....	17,500	.....	.....	6,500		
6	3	.....	.....	15,000	.....	.....	.....	.....	.....	7,000	200	
9	6	0	12,288	7,500	3,200	12,288	20,000	200	384	12,500	3,200	6,144
12	9	0	12,288	6,250	3,200	6,144	8,000	800	192	10,000	6,400	12,288
15	12	400	12,288	6,500	3,200	3,072	12,500	400	96	8,750	9,600	6,144
18	15	800	6,144	7,500	6,400	3,072	18,500	800	192	15,000	4,800	6,144
21	18	800	12,288	10,000	12,000	1,536	11,250	800	1,536	10,000	4,800	6,144
24	21	200	12,288	8,250	6,400	6,144	13,250	200	384	12,500	4,800	6,144
27	24	200	12,288	8,750	3,200	6,144	11,250	200	384	7,500	3,200	3,072
30	27	200	6,144	8,000	3,200	12,288	6,750	200	768	8,500	1,600	3,072
33	30	200	1,536	10,000	3,200	6,144	10,000	200	384	8,000	1,600	3,072
39	35	200	768	12,500	800	6,144	9,500	200	384	14,000	800	3,072
	43	200	1,536	.....	0	3,072	.....	200	768	.....	800	3,072
	50	0	384	.....	400	3,072	.....	0	384	.....	400	1,536
	54	0	384	.....	400	3,072	.....	0	768	.....	400	768

Rabbit 1 is an example of low precipitin and abundant lysin production.

Rabbit 5 shows a fairly abundant output of precipitin and lysin, the latter running a rather irregular course.

Rabbit 6 is an example of low production of both lysin and precipitin.

The figures in the tables give the highest active dilution of the rabbit serum in the lysin tests, and under precipitin the highest dilution

TABLE 3  
LARGE SINGLE DOSE OF THORIUM X SIX DAYS AFTER INJECTION OF SHEEP BLOOD

Days after Injection of Sheep Blood	Rabbit 2			Rabbit 7			Rabbit 10			Rabbit 3			Rabbit 4		
	Precip- itin	Lysin	Leuko- cytes	Precip- itin	Lysin	Leuko- cytes	Precip- itin	Lysin	Leuko- cytes	Precip- itin	Lysin	Leuko- cytes	Precip- itin	Lysin	Leuko- cytes
0	0	192	10,400	0	96	10,000	0	192	11,600	0	96	10,800	0	96	12,800
3	0	24	14,000	0	24	9,600	0	192	9,600	0	96	13,600	0	48	14,000
5	0	3,072	9,800	0	1,536	8,800	0	3,072	10,800	0	3,072	8,200	0	8,072	8,600
6	0	3,072	.....	0	.....	.....	200	6,144	.....	0	3,072	.....	0	1,536	.....
7	500	3,072	4,200	200	3,072	3,000	2,000	6,144	8,200	1,200	3,072	4,600	500	1,536	4,600
8	800	6,144	3,600	1,600	3,072	2,800	2,000	6,144	5,400	1,600	3,072	3,600	500	3,072	2,600
9	1,600	6,144	2,600	1,600	6,144	2,200	2,000	6,144	2,800	1,600	6,144	3,000	800	6,144	2,400
10	3,200	6,144	1,700	3,200	6,144	1,500	2,000	6,144	1,800	1,600	6,144	1,400	1,600	6,144	1,800
11	3,200	6,144	1,000	3,200	6,144	1,500	4,800	6,144	1,700	4,800	6,144	1,400	3,200	6,144	1,700
13	6,400	3,072	2,000	1,600	6,144	1,200	3,200	6,144	2,000	3,200	3,072	2,100	6,400	3,072	1,800
15	.....	.....	1,400	6,400	3,072	1,100	3,200	6,144	2,700	1,600	3,072	2,200	12,800	3,072	1,000
18	3,200	1,536	1,200	6,400	3,072	2,000	6,400	6,144	2,700	1,600	768	4,000	Died		
21	3,200	1,536	1,100	3,200	3,072	2,900	6,400	6,144	2,400	1,600	768	3,400			
24	3,200	768	1,700	800	1,536	3,000	3,200	3,072	4,200	800	768	4,100			
27	400	768	2,200	800	1,536	5,600	3,200	3,072	6,400	800	768	5,200			
30	200	768	2,700	800	1,536	5,300	3,200	3,072	5,200	800	768	6,000			
35	200	768	2,000	640	1,536	4,500	1,600	1,536	3,900	800	768	6,200			
40	160	384	.....	640	1,536	.....	800	768	.....	400	768				
46	160	384	2,600	640	768	5,100	640	768	4,400	320	768	7,200			
49	160	192	3,000	640	384	5,200	640	768	4,400	320	384	9,200			
57	160	192	4,000	640	384	8,000	.....	.....	.....	320	384				
63	160	192	4,800	320	192	8,000	320	768	4,600	320	384				

Thorium X, one third  
of lethal dose

of sheep blood in which the rabbit serum caused precipitate by the contact method after two hours at room temperature. The lysin mixtures contained 0.2 c c of 5% suspension of washed corpuscles, 0.006 c c guinea-pig serum as complement, heated rabbit serum and salt solution, the total quantity of each mixture being 0.6 c c. The lysin mixtures were incubated for two hours and then put into the icebox until the next morning.

In the next experiment about one-half the lethal dose was given in a single intravenous injection at the same time as the sheep blood was injected into the abdomen. The leukocytes were reduced and the formation of precipitin restrained, but in neither case as much as in the first experiment; lysin was produced freely.

A series of 13 rabbits, all young and healthy, were injected intravenously, daily or every other day, with small doses of thorium X, mostly  $\frac{1}{500}$  of the lethal quantity, in some cases  $\frac{1}{200}$ . These injections were started 48 hours before the sheep blood was injected in the usual way and continued until long past the high point of antibody production. The results are illustrated in table 2. In no case was there any marked change in the number of leukocytes; in 9 animals the production of lysin was abundant, in 4 the titer remained rather low; in all but 2 of the 13 rabbits the amount of precipitin in the blood was comparatively insignificant.

In still another series of 12 young and healthy rabbits, about one third of the lethal dose of thorium X was given on the sixth day after the intraperitoneal injection in each rabbit of 25 c c of sheep blood. The purpose of this experiment was to determine what effect if any thorium X would have when given after the production of antibodies was well under way. The results are illustrated in table 3. We note that while the leukocytes were greatly reduced by the thorium injection, there was no definite and clearly recognizable effect on either the amount of lysin and precipitin in the blood or on the length of time of their persistence.

#### SUMMARY AND DISCUSSION

In rabbits treated with thorium X in the early stages of antibody production, under the conditions described, the amount of precipitin in the blood may be reduced even when there is no definite reduction in the leukocytes in the peripheral blood. This result indicates that thorium X may act on the mechanism of production rather than on the precipitin itself, especially when taken in conjunction with the fact

that thorium X seems to have no effect on the amount of precipitin in the blood if injected when the precipitin-production is well under way, that is, on the sixth day or so after the injection of the antigen. From our results it is uncertain whether the thorium X as given in these experiments exercised any definite effect on the formation of lysin. In this respect thorium X would appear to differ in effect from benzene<sup>13</sup> and the roentgen ray, which have been found to restrain the output of lysin as well as precipitin. It is noteworthy also that thorium X, like benzene and the roentgen ray, seems to be without effect on the antibody content of the blood when introduced near the height of the curve; but that unlike the other two agents, it causes leukopenia as promptly at this time as earlier. Further and more diversified experiments are required to determine whether these are constant and fundamental differences in the actions of agents which disturb in some way the production of antibodies at the same time they destroy leukocytes, marrow and lymphoid cells.

<sup>13</sup> Hektoen: *Jour. Infect. Dis.*, 1916, 19, p. 69; 1915, 17, p. 415; 1918, 22, p. 28.